REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 1, 63, and 71 have been amended and claim 22 has been canceled. Therefore, claims 1-21, 23, 30, 40-42, and 47-71 are pending.

Rejection under 35 U.S.C. § 103(a)

Claims 1-23, 30, 40-42 and 47-71 were rejected under 35 U.S.C. 103(a) as unpatentable over WO 99/13816 in combination with Tardi (US 2003/0124181). This rejection is respectfully traversed.

WO 99/13816 discusses a method for loading liposomes with camptothecins. At page 3 of the Office action, the Eaxminer notes that what is lacking in WO is the loading of active agents other than camptothecins.

Also at page 3 of the Office action, the Examiner states that Tardi teaches that therapeutic agents with one or more ionizable moiety can be loaded using pH gradients. It is noted that Tardi primarily focuses on the preparation of liposomes from negatively charged lipids that are stable in the blood (please see Tardi at the Abstract, and at paragraphs 0013-0020). At paragraphs 0072-0083, Tardi does generally discuss both the passive and active loading of liposomes. However, gradient loading is not the focal point of the Tardi invention.

Independent claims 1, 63, and 71 recite the following:

> (a) contacting liposomes in an aqueous solution of up to 50 mM of an acid with an anthracycline chemotherapeutic agent, at a temperature wherein the protonated form of the anthracycline chemotherapeutic agent is charged and is not capable of permeating the membrane of the liposomes, and wherein the unprotonated form of the anthracycline chemotherapeutic agent is uncharged and is capable of permeating the membrane of the liposomes;
>
> (b) actively loading the liposomes with the anthracycline chemotherapeutic agent by raising the pH of the solution to 5.0 or above;
>
> (c) cooling the solution to a temperature at which the unprotonated form of the anthracycline chemotherapeutic agent is not capable of permeating the membrane of the liposomes; and
>
> (d) contacting the solution with a weak base that is an ammonium salt or an alkyl amine, in an amount effective to

> raise the pH of the internal liposome to provide gradient loaded liposomes.

The Examiner has taken the position that it would have been obvious from the teaching of Tardi to load the anthracycline chemotherapeutic agent recited in the instant claims using the method discussed in WO 99/13816.

The Supreme Court set out the analysis for patentability under 35 USC 103(a): the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined (*see, e.g., Graham v. John Deere Co.*, 383 U.S. 1 (1966) and *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007)).

The instant claims include a quenching step (d), which recites contacting the solution with a weak base that is an ammonium salt or an alkyl amine, in an amount effective to raise the pH of the internal liposome to provide gradient loaded liposomes. As discussed at page 14 of the specification,

> Drug loading via the pH gradient includes a low pH in the internal aqueous space of the liposomes, and this internal acidity is, by design, incompletely neutralized during the drug loading process. This residual internal acidity can cause chemical instability in the liposomal preparation (e.g., lipid hydrolysis), leading to limitations in shelf life. To quench this residual internal acidity, membrane permeable bases, such as amines (e.g., ammonium salts or alkyl-amines) can be added following the loading of the pharmaceutical agent in an amount sufficient to reduce the residual internal acidity to a minimum value (for example, pH at or above 4).

This quenching step represents a significant difference between the teaching of Tardi and the instant claims.

Tardi does not teach the preparation of any liposomes using the quenching step (d). Accordingly, the final liposomes prepared by Tardi maintain a low pH in the internal aqueous space that helps keep the drug loaded inside the liposome. At paragraph 0076 Tardi teaches that "Once the drug moves inside the liposome, the pH of the interior results in a charged drug

state, which prevents the drug from permeating the lipid bilayer, thereby entrapping the drug in the liposome." Additionally in paragraph 0080, Tardi teaches that "Conversion of moiety to a charged form causes the drug to remain encapsulated within the liposome." Accordingly, Tardi teaches that it is critical to maintain the low pH in the internal aqueous space after active loading of the liposome in order to keep the therapeutic agent trapped inside.

Applicant respectfully submits that one skilled in the art would not have had a reasonable belief that the anthracycline chemotherapeutic agent generally discussed in Tardi could have been loaded using the method of WO 99/13816 to provide a loaded liposome that would retain the anthracycline chemotherapeutic agent following the quenching procedure, since Tardi teaches that the low pH in the interior of the liposome is critical for keeping the agent inside the liposome following gradient loading. Thus, Tardi teaches away from employing the quenching step (d) recited in the instant claims. Accordingly, it is respectfully submitted that one skilled in the art would not have been motivated to combine the teaching of WO 99/13816 and Tardi as suggested by the Examiner. It is also respectfully submitted that one skilled in the art would not have had a reasonable expectation that the liposomes discussed by Tardi would have effectively retained the anthracycline chemotherapeutic agent if the residual internal acidity was quenched following loading using the method of WO 99/13816.

Since there was no motivation to combine the cited documents as suggested by the Examiner, and because there would not have been a reasonable expectation that the references so combined would have provided liposomes that would have stayed loaded, it is respectfully submitted that the Examiner has not established a *prima facie* case of obviousness over the disclosure of WO 99/13816 in combination with Tardi. Accordingly, withdrawal of the rejection is appropriate and is requested.

It is noted that the inclusion of claim 7 in this rejection is believed to have been an error. At page 4 of the Office action, the Examiner admitted that these cited documents do not teach sphingomyelin as a liposome-forming lipid. Accordingly, the cited documents do not teach all elements of claim 7. Thus, claim 7 can not be *prima facie* obvious over the cited documents. Additionally, at page 3 of the Office action the Examiner states that "since it is a commonly used lipid in the liposome formations, it would have been obvious to one of ordinary skill in the art to use this lipid with a reasonable expectation of success." It is respectfully submitted that the Examiner has provided no evidence to support this conclusion. Since the

Examiner provided no evidence to support this conclusion, Applicant submits that the Examiner is taking "official notice" that "it would have been obvious to one of ordinary skill in the art to use this lipid with a reasonable expectation of success." If the Office maintains the rejection of claim 7 over WO 99/13816 in combination with Tardi, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support this finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements to support the conclusion that it would have been obvious to one of ordinary skill in the art to use this lipid with a reasonable expectation of success.

It is also noted that the inclusion of claim 49 in this rejection is believed to have been an error. At page 5 of the Office action, the Examine admitted that these cited documents do not teach the change of the pH using methylamine. Accordingly, the cited documents do not teach all elements of claim 49. Thus, claim 49 can not be *prima facie* obvious over the cited documents.

It is also noted that the inclusion of claims 52-57 in this rejection is believed to have been an error. The Examiner has not suggested that the cited documents teach dehydration of liposomes in the presence of cryoprotectants (also, please see section 5 of the Office action). Accordingly, the cited documents do not teach all elements of claims 52-57. Thus, claims 52-57 can not be *prima facie* obvious over the cited documents.

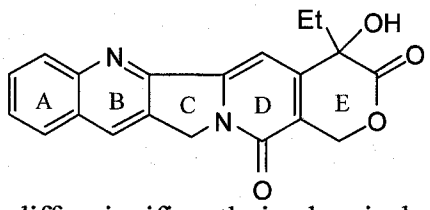
Claims 1-23, 30, 40-42 and 47-71 were rejected under 35 U.S.C. 103(a) as unpatentable over EP 0 719 546 in view of WO 99/13816. This rejection is respectfully traversed.

WO 99/13816 discusses methods for loading liposomes with camptothecins.

EP 0 719 546 discusses gradient loading of liposomes – however, EP 0 719 546 does not disclose a process that includes steps (c) and (d) above. Additionally, EP does not discuss loading any camptothecin compounds.

The Examiner has not provided any explanation regarding why one skilled in the art would have had a reasonable expectation that the disclosure of WO 99/13816 could have been combined with the disclosure of EP 0 719 546 as suggested by the Examiner. The camptothecins

discussed in WO 99/13816 comprise the following ring system, wherein the lactone ring E can be open or closed (please see WO 99/13816 at pages 8-10):



These camptothecin compounds differ significantly in chemical structure from the agents that were loaded in EP 0 719 546. The camptothecin compounds also have significantly different physical properties (e.g. molecular weights, melting points, lipophylicities, solubilities, etc.) from the anthracycline chemotherapeutic agents recited in the instant claims. Because the camptothecins discussed in WO99/13816 differ significantly from the compounds discussed in EP 0 719 546, it is respectfully submitted that one skilled in the art would not have had a reasonable expectation that that compounds discussed in EP 0 719 546 would be operative in the loading methods discussed in WO 99/13816. This is especially true, since the loading process discussed in EP 0 719 546 does not include steps (c) and (d) recited in the claims. Accordingly, the Examiner has not established that the instant claims are *prima facie* obvious over WO 99/13816 in combination with EP 0 719 546. Withdrawal of the rejection is appropriate and is requested.

Additionally, it is submitted that the Examiner has not provided any evidence to support his conclusion that "it would have been obvious to one of ordinary skill in the art to load an active agent at an acidic medium and then relative to the liposome interior and then change the pH of the exterior to basic pH such that the active agent remains entrapped." (Office action at page 4 lines 7-9). As discussed above, there are significant differences between the agents discussed in the two cited documents. Accordingly, one skilled in the art would not have had a reasonable belief that the agents that were loaded in EP 0 719 546 would behave like the structurally distinct camptothecins discussed in WO99/13816.

Additionally, as discussed above, Tardi generally teaches that the low pH in the interior of the liposome is critical for keeping the agent inside the liposome following active loading. This suggests that one skilled in the art would not have reasonably concluded that the anthracycline chemotherapeutic agents recited in the instant claims would remain in the

liposomes if the internal acidity was quenched. Thus, there is no evidence of record to support the Examiner's conclusion that "it would have been obvious to one of ordinary skill in the art to load an active agent at an acidic medium and then relative to the liposome interior and then change the pH of the exterior to basic pH such that the active agent remains entrapped." In fact, it is respectfully submitted the structural dissimilarity of the respective compounds and the discussion of Tardi suggest that this statement is false. Accordingly, since there is no evidence of record to support this conclusion, Applicant submits that the Examiner is taking "official notice" that "it would have been obvious to one of ordinary skill in the art to load an active agent at an acidic medium and then relative to the liposome interior and then change the pH of the exterior to basic pH such that the active agent remains entrapped." If the Office maintains the rejection over WO 99/13816 in combination with EP 0 719 546, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support this finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the conclusion that one of ordinary skill in the art would be motivated to load any active agent in the methods of WO 99/13816 with a reasonable expectation of success.

At page 3 of the Office action, regarding phosphatidylglycerol, the Examiner states that "since it is the commonly used negatively charged lipid to provide negative charge to the liposomes, it would have been obvious to one of ordinary skill in the art to include this phospholipid with a reasonable expectation of success." It is respectfully submitted that the Examiner has provided no evidence to support this conclusion. Why would one skilled in the art have even considered phosphatidylglycerol; why would one skilled in the art have wanted to use it; what effect would one skilled in the art have assumed it would have had in the particular systems recited in the claims? Since the Examiner provided no evidence to support this conclusion, Applicant submits that the Examiner is taking "official notice" that "it would have been obvious to one of ordinary skill in the art to use this lipid with a reasonable expectation of success." If the Office maintains the rejection, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support this finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or

declaration setting forth specific factual statements to support the conclusion that it would have been obvious to one of ordinary skill in the art to include this phospholipid with a reasonable expectation of success.

It is noted that the inclusion of claim 7 in this rejection is believed to have been an error. At page 4 of the Office action, the Examine admitted that these cited documents do not teach sphingomyelin as a liposome-forming lipid. Accordingly, the cited documents do not teach all elements of claim 7. Thus, claim 7 can not be *prima facie* obvious over the cited documents.

It is also noted that the inclusion of claim 49 in this rejection is believed to have been an error. At page 5 of the Office action, the Examine admitted that these cited documents do not teach the change of the pH using methylamine. Accordingly, the cited documents do not teach all elements of claim 49. Thus, claim 49 can not be *prima facie* obvious over the cited documents.

It is also noted that the inclusion of claims 52-57 in this rejection is believed to have been an error. The Examiner has not suggested that the cited documents teach dehydration of liposomes in the presence of cryoprotectants (also, please see section 5 of the Office action). Accordingly, the cited documents do not teach all elements of claims 52-57. Thus, claims 52-57 can not be *prima facie* obvious over the cited documents.

Claims 7 and 49 were also rejected under 35 USC § 103(a) as being as being unpatentable over WO 99/13816 in combination with Tardi OR over EP 0 719 546 in combination with WO 99/13816, further in view of Webb (5,814,335).

At page 4, bridging to page 5 of the Office action the Examiner stated that what is lacking in WO 99/13816, Tardi, and EP 0 719 546 is the use of sphingomyelin as a liposome forming lipid. As discussed above, independent claims 1, 63, and 71 are not *prima facie* obvious over WO 99/13816, Tardi, and EP 0 719 546 as applied earlier in the Office action. Thus, more is lacking from the primary documents than the use of sphingomyelin. It is respectfully submitted that the secondary document Webb, as applied by the Examiner, does not cure the deficiencies discussed above, since it was only cited with respect to sphingomyelin as a liposome forming lipid. Accordingly, claims 7 and 49 are not obvious over the disclosures of WO 99/13816 in combination with Tardi or over EP 0 719 546 in combination with WO 99/13816, further in view

of Webb (5,814,335). Withdrawal of this rejection is respectfully requested. It is not clear why claim 49 was included in this rejection relating to sphingomyelin. Clarification is requested.

Additionally at page 5, the Examiner states that neither EP nor WO teaches "the change of the pH of the external medium by using methylamine," and that "The use of methylamine to change the pH of the external medium would have been obvious to one of ordinary skill in the art since Webb teaches the creation of a pH gradient using methyl amine (columns 7 and 8)." As discussed above, independent claims 1, 63, and 71 are not *prima facie* obvious over WO 99/13816, Tardi, and EP 0 719 546 as applied earlier in the Office action. Thus, more is lacking from the primary documents than the use of methylamine as a base. It is respectfully submitted that the secondary document Webb, as applied by the Examiner, does not cure the deficiencies, since it was only cited with respect to the use of methylamine. Accordingly, it is submitted that claims 7 and 49 are not obvious over the disclosures of WO 99/13816 in combination with Tardi or over EP 0 719 546 in combination with WO 99/13816, further in view of Webb (5,814,335). Withdrawal of this rejection is respectfully requested.

In addition to the fact that the rejection should be withdrawn for the reason discussed above, it is respectfully submitted that methyl amine/methyl ammonium gradient discussed in Webb performs a significantly different function that the methyl amine recited in claim 49. Webb discusses the use of a methyl amine/methyl ammonium gradient to actively load the neutral form of a protonatable therapeutic agent (column 7, lines 40-64) into a liposome. Claim 49 is directed to the method of claim 1 wherein a weak base selected from the group of methyl amine, ethyl amine, diethyl amine, ethylene diamine, and propyl amine is used in step (d) to quench the residual acidity inside the liposomes after loading in the presence of an acid.

Webb does not use the methylamine to quench residual acid in a loaded liposome. Rather, Webb uses methylamine to establish a pH gradient (as noted by the Examiner at page 5, lines 6-7 of the Office action). Thus, methyl amine is used by Webb for the opposite purpose than it is used for in the claimed methods. Accordingly, it is submitted that one skilled in the art would not have found any motivation in Webb to use methylamine as recited in claim 49. For this additional reason it is submitted that claims 7 and 49 are not obvious over the disclosures of WO 99/13816 in combination with Tardi or over EP 0 719 546 in combination with WO 99/13816, further in view of Webb (5,814,335) as suggested by the Examiner. Withdrawal of

this rejection is respectfully requested. It is not clear why claim 7 was included in this rejection relating to methylamine. Clarification is requested.

Claims 52-57 were rejected under 35 USC § 103(a) as unpatentable over WO 99/13816 in combination with Tardi OR over EP 0 719 546 in combination with WO 99/13816, further in view of Clerc (5,939,096).

At page 5 of the Office action the Examiner stated that Clerc teaches liposomes can be dehydrated for storage in the presence of cryoprotectants. As discussed above, independent claims 1, 63, and 71 are not *prima facie* obvious over WO 99/13816, Tardi, and EP 0 719 546 as applied earlier in the Office action. Thus, more is lacking from the primary documents than the dehydration of liposomes in the presence of cryoprotectants. It is respectfully submitted that the secondary document Clerc, as applied by the Examiner, does not cure the deficiencies discussed above, since it was only cited with respect to the dehydration of liposomes in the presence of cryoprotectants. Accordingly, the claims 52-57 are not obvious over the disclosures of WO 99/13816 in combination with Tardi or over EP 0 719 546 in combination with WO 99/13816, further in view of Clerc (5,939,096). Withdrawal of this rejection is respectfully requested.

The Examiner has provisionally rejected claims 1-23, 30, 40-42 and 47-71 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-28, 30-31, 33, 40-42 and 47-71 of copending Application No. 10/723,431.

Independent claims 1, 63, and 71 have been amended to recite "contacting liposomes in an aqueous solution of up to 50 mM" in step (a). This amendment is believed to obviate the Examer's ground for rejection. Accordingly, withdrawal of this rejection is respectfully requested.

If the Examiner maintains this rejection, Applicant will wait until otherwise patentable subject matter is identified in both cases before determining if a terminal disclaimer is appropriate, since this is a provisional rejection.

Claims 1-23, 30, 40-42 and 47-71 were rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 30-31 and 35-64 of U.S. Patent No. 6,740,335 in combination with Tardi (US 2003/0124181). This rejection is respectfully traversed.

US Patent 6,740,335 is related to WO 99/13816. In the instant Office action, the Examiner rejected the pending claims under 35 USC 103(a) as obvious over WO 99/13816 in

combination with Tardi. It is respectfully submitted that the instant claims are non-obvious over the claims of US 6,740,335 in combination with Tardi for the reasons presented above in response to the 35 USC 103(a) rejection over WO 99/13816 in combination with Tardi. Accordingly, withdrawal of the obviousness type double patenting rejection over claims 30-31 and 35-64 of US Patent 6,740,335 in combination with EP 0 719 546 is appropriate and is requested.

CONCLUSION

In light of the above remarks and amendments, withdrawal of the outstanding rejections and allowance of the pending claims 1-21, 23, 30, 40-42, and 47-71 is requested. The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

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By their Representatives,

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